Study uncovers gene that doubles risk of death from COVID-19

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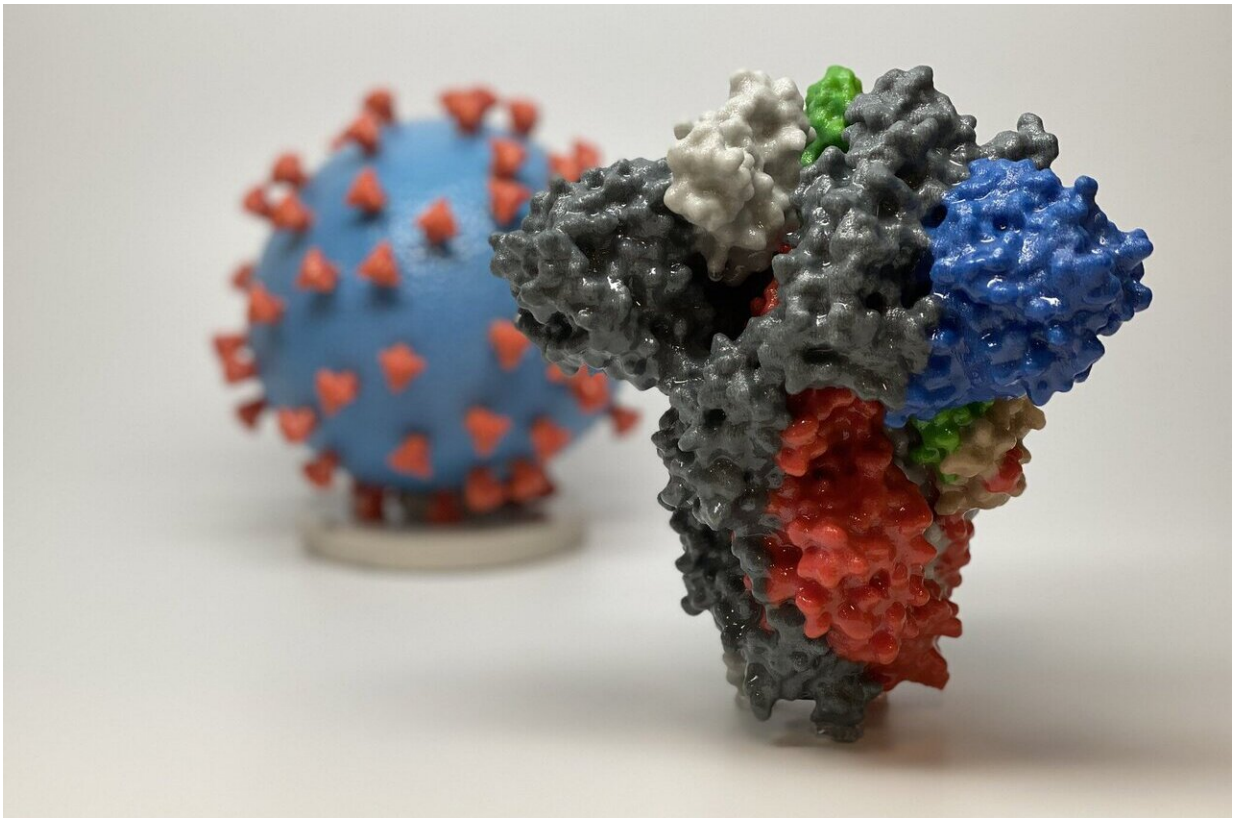

3D print of a spike protein of SARS-CoV-2, the virus that causes COVID-19—in front of a 3D print of a SARS-CoV-2 virus particle. The spike protein (foreground) enables the virus to enter and infect human cells. On the virus model, the virus surface (blue) is covered with spike proteins (red) that enable the virus to enter and infect human cells. Credit: NIH

Radcliffe Department of Medicine researchers have identified the gene responsible for doubling the risk of respiratory failure from COVID-19. Sixty percent of people with South Asian ancestry carry the high-risk genetic signal, partly explaining the excess deaths seen in some UK communities, and the impact of COVID-19 in the Indian subcontinent.

Previous work has already identified a stretch of DNA on chromosome 3 which doubled the risk of adults under 65 of dying from COVID. However, scientists did not know how this genetic signal worked to increase the risk, nor the exact genetic change that was responsible.

In a study published in *Nature Genetics*, a team lead by Profs. James Davies and Jim Hughes at the University of Oxford's MRC Weatherall Institute of Molecular Medicine used cutting edge technology to work out which gene was causing the effect, and how it was doing so.

Study co-lead Prof Jim Hughes, Professor of Gene Regulation, said that "the reason this has proved so difficult to work out, is that the previously identified genetic signal affects the "dark matter" of the genome. We found that the increased risk is not because of a difference in gene coding for a protein, but because of a difference in the DNA that makes a switch to turn a gene on. It's much harder to detect the gene which is affected by this kind of indirect switch effect."

The team trained an artificial intelligence algorithm to analyze huge quantities of genetic data from hundreds of types of cells from all parts of the body, to show that the genetic signal is likely to affect cells in the lung. Then using a highly accurate technique they had only just developed, the researchers could zoom down on the DNA at the genetic signal. This examines the way that the billions of DNA letters fold up to fit inside a cell to pinpoint the specific gene that was being controlled by the sequence causing the greater risk of developing severe COVID-19.

Dr. Damien Downes, who led the laboratory work from the Hughes research group, said that "surprisingly, as several other genes were suspected, the data showed that a relatively unstudied gene called LZTFL1 causes the effect."

The researchers found that the higher risk version of the gene probably prevents the cells lining airways and the lungs from responding to the virus properly. But importantly it doesn't affect the immune system, so the researchers expect people carrying this version of the gene to respond normally to vaccines.

The researchers are also hopeful that drugs and other therapies could target the pathway preventing the lung lining from transforming to less specialized cells, raising the possibility of new treatments customized for those most likely to develop severe symptoms.

Study co-lead Prof James Davies, who worked as an NHS consultant in intensive care medicine during the pandemic and is an associate professor of genomics at Oxford University's Radcliffe Department of Medicine, said: "The genetic factor we have found explains why some people get very seriously ill after coronavirus infection. It shows that the way in which the lung responds to the infection is critical. This is important because most treatments have focussed on changing the way in which the immune system reacts to the virus."

Sixty percent of people with South Asian ancestry carried this higher-risk version of the gene compared to 15 percent of those with European ancestry—explaining in part the higher death rates and hospitalisations in the former group. The study also found that 2 percent of people with Afro-Caribbean ancestry carried the higher risk genotype, meaning that this genetic factor does not completely explain the higher death rates reported for black and minority ethnic communities.

Prof Davies explained that "the higher risk DNA code is found more commonly in some black and minority ethnic communities but not in others. Although we cannot change our genetics, our results show that the people with the higher risk gene are likely to particularly benefit from vaccination. Since the genetic signal affects the lung rather than the immune system it means that the increased risk should be canceled out by the vaccine."

More information: Damien J. Downes et al, Identification of LZTFL1 as a candidate effector gene at a COVID-19 risk locus, *Nature Genetics* (2021). DOI: 10.1038/s41588-021-00955-3

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